Organic Letters

Supporting Information to Accompany:

Novel Bryostatin Analogs via an Improved C-Ring Synthesis

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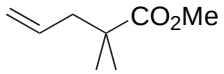
Experimental Section

General: Oxygen- and moisture-sensitive reactions were carried out in flasks heated to 140°C in an oven overnight and cooled under high vacuum (<1 torr). These flasks were then sealed with rubber septa and a positive pressure of dry nitrogen or argon was maintained in them for the duration of the experiment. Correspondingly sensitive liquids were transferred via syringe or cannula through rubber septa. Organic solutions were concentrated on a Büchi rotary evaporator connected to a ChemGlass diaphragm pump, and the resulting residue was exposed to high vacuum (<1 torr) for at least 15 minutes to remove residual solvent.

All commercially available reagents were used without further purification unless otherwise noted. Diethyl ether and tetrahydrofuran were distilled from sodium-benzophenone ketyl prior to use. Acetonitrile, dichloromethane, diisopropylamine, triethylamine and pyridine were distilled from calcium hydride. Toluene was distilled from sodium metal. Flash chromatography grade hexanes were distilled from technical grade hexanes.

Analytical thin-layer chromatography (TLC) was performed by using galss-backed silica plates coated with a 0.2 mm thickness of silica gel 60 F_{254} (Merck), visualized with UV light, *p*-anisaldehyde solution, potassium permanganate solution or ceric ammonium molybdate solution. Chromatography was performed using Kieselgel 60 (230-400 mesh). Infrared spectra were recorded on a Perkin-Elmer 1600 Series Fourier transform spectrometer (FTIR). ^{1}H NMR spectra were recorded using Varian Inova spectrometers, and chemical shifts are reported in ppm downfield of an internal tetramethylsilane ($(CH_3)_4Si$) standard. Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, m = multiplet.



15

To a stirred solution of diisopropylamine (16.82 ml, 120 mmol) in THF (50 ml) was added *n*-butyllithium (48 ml, 2.5 M in hexane) dropwise at -78°C. The mixture was stirred at 0°C for 30 min, cooled again to -78°C, and treated with methyl isobutyrate (22.5 ml, 109 mmol) slowly over 10 min. The reaction mixture was stirred for 1.5 hours at -78°C and 1 hour at -40°C. After addition of allyl bromide (11.8 ml, 135 mmol) dissolved in THF (25 ml) the mixture was allowed to warm up to room temperature overnight. The solution was evaporated without aqueous workup. The formed solid LiBr was removed by chromatographic filtration on silica gel with ether / pentane (1:1). Fractional distillation gave **15** (12.77g, 90%) at bp = 135 → 150°°C as colorless liquid.

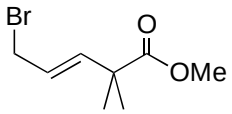
Spectroscopic data:

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (6H, s, CH_3), 2.28 (2H, d, *J* = 7.1 Hz, C17), 3.67 (3H, s, OCH_3), 5.04 (1H, dd, *J* = 0.8 Hz, *J* = 4.0 Hz, C15), 5.08 (1H, d, *J* = 1.0 Hz, *J* = 2.2 Hz, C15), 5.72 (1H, m, C16).

^{13}C NMR (75 MHz, $CDCl_3$) δ (/ppm) 24.79, 42.34, 44.74, 51.68, 117.85, 134.23, 177.94.

FTIR (neat): 2979, 1735, 1472, 1435, 1254, 1208, 1150, 994, 918 cm^{-1}.

HRMS (FAB) *m/z* calculated: ($C_8H_{14}O_2$) 142.0999; observed (M): 142.0994.



15a

To a stirred solution of **15** (14.22 g, 101 mmol) in CCl_4 (80 ml) was added *N*-bromosuccinimide (20 g, 112 mmol) and dibenzoylperoxide (80 mg, 0.33 mmol) in a single portion. The reaction mixture was heated at reflux for 2 hours using an preheated oil bath (105°C). After cooling to room temperature, the mixture was filtered and the residue was washed with CCl_4. The solvent was removed *in vacuo* and the crude material purified using flash chromatography on silica gel with EtOAc/hexane (9/1) yielding the desired allylic bromide **15a** (8.34 g, 74%) as yellow oil.

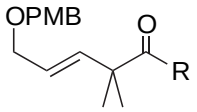
Spectroscopic data:

^{1}H NMR (300 MHz, $CDCl_3$) δ (/ppm) 1.31 (6H, s, CH_3), 3.69 (3H, s, OCH_3), 3.96 (2H, d, *J* = 7.3 Hz, CH_2), 5.77 (1H, dd, C16), 5.97 (1H, d, *J* = 15.6 Hz, C17).

^{13}C NMR (75 MHz, $CDCl_3$) δ (/ppm) 24.77, 32.73, 44.08, 52.21, 124.81, 139.39, 176.31.

FTIR (neat): 2979, 1732, 1470, 1434, 1387, 1263, 1207, 1146, 969, 769, 588 cm^{-1}.

HRMS (FAB) *m/z* calculated: ($C_8H_{13}O_2Br$) 221.0177; observed (M): 221.0162; ($C_8H_{13}O_2{}^{81}Br$) 223.0157; observed (M): 223.0163.



16a R=OMe
16b R=OPMB
16c R=OH

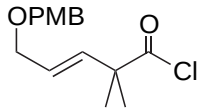
To a suspension of sodium hydride (1.83 g, 45.8 mmol; 60% in mineral oil) in 100 ml anhydrous THF was added a solution of *p*-methoxy benzylalcohol (5.75 g, 41.6 mmol) in THF (25 ml) slowly over 15 minutes at 0°C. The mixture was stirred at room temperature for 45 minutes before a solution of the previously prepared allylic bromide (2.3 g, 10.4 mmol) in 30 ml THF was added over 15 min. The reaction mixture was warmed to 35°C for 6 h. The reaction was cooled to room temperature and quenched with water carefully. The aqueous layer was extracted with Et_2O (2x), then neutralized with 2N HCl, and again extracted with EtOAc (4x). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue on silica gel (EtOAc/hexane 33% - 80%) afforded **16b** (2.03 g, 74%) as yellow oil.
Alternatively the reaction can be quenched with saturated NH_4Cl solution. The aqueous layer was then extracted with Et_2O (3x) and the combined layers were dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (EtOAc 20%) to provide a mixture of **16a** & **16b**, the methyl and *p*-methoxybenzyl esters.

Spectroscopic data:

16a (methyl ester): ^{1}H NMR (300 MHz, $CDCl_3$) δ (/ppm) 1.32 (6H, s, $C(CH_3)_2$), 3.79 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.98 (2H, d, C15), 4.44 (2H, s, $ArCH_2$), 5.05 (2H, s, $ArCH_2$), 5.64 (1H, m, C16), 5.91 (1H, d, C17), 6.87 (2H, d, Ar), 7.26 (2H, d, Ar).
^{13}C NMR (75 MHz, $CDCl_3$) δ (/ppm) 24.92, 44.09, 52.07, 55.26, 70.79, 71.74, 94.00, 113.74, 124.91, 129.47, 130.23, 137.62, 159.16, 176.75.
HRMS (FAB) *m/z* calculated: ($C_{16}H_{22}O_4$) 278.1518; observed (M): 278.1526.

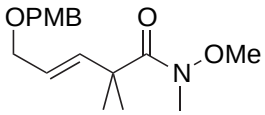
16b (PMB ester): ^{1}H NMR (300 MHz, $CDCl_3$) δ (/ppm) 1.31 (6H, s, $C(CH_3)_2$), 3.67 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.99 (2H, d, C15), 4.44 (2H, s, $ArCH_2$), 5.63 (1H, m, C16), 5.90 (1H, d, C17), 6.88 (4H, d, Ar), 7.27 (4H, d, Ar).

16c ^{1}H NMR (300 MHz, $CDCl_3$) δ (/ppm) 1.33 (6H, s, $C(CH_3)_2$), 3.80 (3H, s, OCH_3), 4.01 (2H, dd, *J* = 1.1, 5.9 Hz, C15), 4.44 (2H, s, $ArCH_2$), 5.71 (1H, dd, C16), 5.93 (1H, d, C17), 6.88 (2H, d, *J* = 8.6 Hz, Ar), 7.27 (2H, d, *J* = 8.8 Hz, Ar).
^{13}C NMR (75 MHz, $CDCl_3$) δ (/ppm) 24.69, 43.88, 55.26, 70.17, 71.86, 113.76, 125.53, 129.50, 130.17, 136.91, 159.17
FTIR (neat): 3370, 2978, 2864, 1702, 1612, 1513, 1469, 1362, 1302, 1249, 1173, 1035, 975, 820 cm^{-1}.
HRMS (FAB) *m/z* calculated: ($C_{15}H_{20}O_4$) 264.1362; observed (M): 264.1362.



3

To a stirred solution of acid **16c** (133 mg, 0.5 mmol) in anhydrous Et_2O (6 ml) and cooled to 0°C, was added sodium hydride (240 mg, 6.0 mmol; 60% in mineral oil) in a single portion. The mixture was stirred for 30 minutes at 0°C and then oxalyl chloride (0.26 ml, 3.0 mmol) was added in a single portion. The resulting mixture was allowed to warm to room temperature and stirring was continued for 2 h. The mixture was then concentrated *in vacuo* and the resulting oil used without further purification.

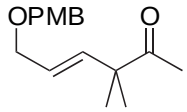


17

To a stirred solution of methyl and *p*-methoxybenzyl esters **16a** and **16b** (6.56 g, 23.55 mmol) in THF (20 ml), was added *N*,*O*-dimethylhydroxylamine hydrochloride (3.68 g, 37.7 mmol), followed by dropwise addition of phenylmagnesium bromide (2M in THF, 18.25 ml, 36.5 mmol) at -20°C. To the reaction mixture was subsequently added phenylmagnesium bromide (18.25 ml, 36.5 mmol) over 45 min. Stirring was continued for 1 hour at -10°C. The reaction was quenched with saturated NH_4Cl and diluted with Et_2O. The aqueous layer was extracted with EtOAc (3x) and the combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (EtOAc/hexane 1/3) to provide Weinreb amide **17** (6.54 g, 90%) as colorless oil.

Spectroscopic data:

^{1}H NMR (300 MHz, $CDCl_3$) δ (/ppm) 1.33 (6H, s, $C(CH_3)_2$), 3.16 (3H, s, CH_3), 3.55 (3H, s, NCH_3), 3.81 (3H, s, OCH_3), 4.00 (2H, d, *J* = 4.1 Hz, C15), 4.45 (2H, s, $ArCH_2$), 5.62 (1H, dd, C16), 5.93 (1H, d,
J = 5.9 Hz, C17), 6.88 (2H, d, *J* = 8.8 Hz, Ar), 7.25 (2H, d, *J* = 7.1 Hz, Ar).
^{13}C NMR (75 MHz, $CDCl_3$) δ (/ppm) 25.41, 33.67, 44.21, 55.26, 60.63, 70.48, 71.81, 113.73, 124.03, 129.34, 130.33, 138.43, 159.14.
FTIR (neat): 2931, 2839, 2358, 1640, 1606, 1512, 1462, 1356, 1242, 1171, 1103, 1069, 1031, 993, 816, 761 cm^{-1}.
HRMS (FAB) *m/z* calculated: ($C_{17}H_{25}NO_4$) 307.1784;
($C_{16}H_{22}NO_4$, M^+-CH_3) 292.1549; observed: 292.1559;
($C_{16}H_{23}NO_3$), M^+-OCH_3) 276.1600; observed: 276.1599.

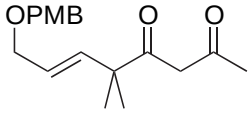


10

A solution of Weinreb amide **17** (5.82 g, 18.1 mmol) in THF (100 ml) was cooled to -78°C then treated with methyllithium (1.4 M in Et_2O, 17.47 ml, 24.5 mmol). Stirring was continued for 1 hour at -78°C, and the reaction was quenched with saturated NH_4Cl, and diluted with Et_2O. The aqueous layer was extracted with EtOAc (3x) and the combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (EtOAc/hexane 1/4) to provide methyl ketone **10** (4.89 g, 99%) as a colorless oil.

Spectroscopic data:

^{1}H NMR (300 MHz, $CDCl_3$) δ (/ppm) 1.24 (6H, s, $C(CH_3)_2$), 2.12 (3H, s, CH_3), 3.81 (3H, s, OCH_3), 4.01 (2H, d, *J* = 5.6 Hz, C15), 4.44 (2H, s, $ArCH_2$), 5.68 (1H, dd, C16), 5.80 (1H, d, *J* = 5.9 Hz, C17), 6.88 (2H, d, *J* = 8.5 Hz, Ar), 7.27 (2H, d, *J* = 8.3 Hz, Ar).
^{13}C NMR (75 MHz, $CDCl_3$) δ (/ppm) 23.84, 25.52, 50.18, 55.26, 70.29, 71.90, 100.25, 113.79, 126.41, 129.40, 130.18, 137.28, 159.22, 211.14.
FTIR (neat): 2970, 2839, 2356, 1707, 1611, 1512, 1464, 1354, 1301, 1278, 1172, 1123, 1100, 1034, 976, 820 cm^{-1}.
HRMS (FAB) *m/z* calculated: ($C_{16}H_{22}O_3$) 262.1569; observed (M): 262.1575



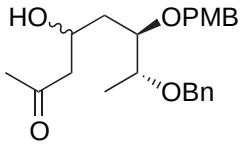
11

a) To a stirred solution of diisopropylamine (0.21 ml, 1.5 mmol) in THF (3 ml) was added *n*-butyllithium (0.93 ml, 1.6 M in hexane) dropwise at -78°C. The mixture was allowed to warm to 0°C and stirred for 30 min, then cooled again to -78°C, and a solution of acetone (0.11 ml, 1.5 mmol) in THF (1 ml) was added dropwise. The acetone used was dried over 4Å molecular sieves for several days and was dried again over 4Å molecular sieves in THF solution immediately prior to use. After stirring for 20 minutes, the mixture was treated with a solution of acid chloride **3** (0.5 mmol) in 2 ml THF and stirring was continued at -78°C for 1 h. The reaction was quenched with saturated NH_4Cl and warmed up to room temperature and diluted with Et_2O. The aequeous layer was extracted with EtOAc (3x) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (EtOAc/hexane 1/2) yielded *β*-diketone **11** (117 mg, 77%) as an orange oil.

Spectroscopic data:

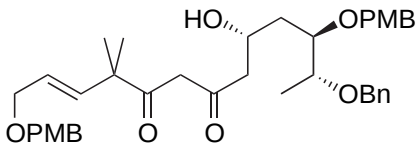
^{1}H NMR (300 MHz, $CDCl_3$) δ (/ppm) 1.27 (6H, s, $C(CH_3)_2$), 2.04 (3H, s, C22), 3.80 (3H, s, OCH_3), 4.00 (2H, d, *J* = 5.6 Hz, C15), 4.45 (2H, s, $ArCH_2$), 5.58 (1H, s, C20), 5.69 (1H, dd, C16), 5.83 (1H, d, *J* = 5.9 Hz, C17), 6.87 (2H, d, *J* = 8.3 Hz, Ar), 7.26 (2H, d, *J* = 6.6 Hz, Ar);

^{13}C NMR (75 MHz, $CDCl_3$) δ (/ppm) 23.35, 24.58, 45.06, 55.22, 70.33, 71.82, 96.90, 113.73, 125.42, 129.40, 130.18, 135.68, 138.09, 159.16, 190.01, 199.35.
FTIR (neat): 3480, 2965, 2847, 1716, 1699, 1606, 1505, 1454, 1353, 1303, 1243, 1167, 1100, 1032, 973, 821 cm^{-1}.
HRMS (FAB) *m/z* calculated: ($C_{18}H_{24}O_4$) 304.1675; observed (M): 304.1683; ($C_{10}H_{15}O_3$, M^+- PMB) 183.1021; observed (M): 183.1051.



18

To a stirred solution of diisopropylamine (0.21 ml, 1.5 mmol) in THF (3 ml) was added *n*-butyllithium (0.93 ml, 1.6 M in hexane) dropwise at -78°C. The mixture was warmed to 0°C and stirred for 30 minutes, then cooled again to -78°C, and treated with a solution of acetone (0.11 ml, 1.5 mmol) in THF (1 ml). The acetone used was dried over 4Å molecular sieves for several days and was dried again over 4Å molecular sieves in THF solution immediately prior to use. After recooling to –78°C and stirring for 20 minutes, aldehyde **4** (164 mg, 0.5 mmol) was added dropwise and stirring was continued for 15 minutes. The reaction was quenched by addition of saturated NH_4Cl and the mixture was warmed to room temperature and diluted with Et_2O. The mixture was diluted with Et_2O and the layers separated. The aqueous layer was then extracted with EtOAc (3x). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexane 1/2) provided **18** (169 mg, 87 %). The diastereoselectivity was determined to be 81%, favoring the desired isomer, after coupling with acid chloride **3** and cyclization to pyranone **12**.



19

From **11**: To a stirred solution of diisopropylamine (1.19 ml, 8.48 mmol) in THF (13 ml) was added *n*-butyllithium (4.08 ml, 8.16 mmol, 2.0 M in hexane) dropwise at -78°C. The mixture was warmed to 0°C and stirred for 30 minutes, then a solution of β-diketone **11** (2.30 g, 8.77 mmol) in THF (13 ml) was added slowly over 10 minutes. After stirring for 1 hour at 0°C, the mixture was cooled to -78°C and aldeyde **4** (1.21 g, 3.69 mmol) was added in a single portion. Stirring was continued for 30 minutes at -78°C and the reaction mixture was then quenched with saturated NH_4Cl solution, allowed to warm to room temperature, and diluted with Et_2O. The mixture was extracted with EtOAc (3x) and the combined organics were dried over $MgSO_4$ and concentrated *in vacuo.* Flash chromatography on silica gel (EtOAc/hexane 1/2) afforded the aldol **19** (1.51 g, 65 %) as

an orange oil. The ratio of the two diastereomers was determined after cyclization to pyranone **12**, and was 1.45:1 favoring the desired isomer.

From **18**: To a stirred solution of diisopropylamine (0.46 μL, 0.204 mmol) in THF (0.5 ml) was added *n*-butyllithium (0.128 ml, 0.204 mmol, 1.6M in hexanes) dropwise at -78°C. The mixture was warmed to 0°C and stirred for 30 min, then cooled again to -78°C, and treated with a solution of *β*-hydroxy ketone **18** (42.0 mg, 0.0662 mmol) in THF, (1 ml) dropwise. After stirring for 20 minutes at -78°C the mixture was treated with a solution of acid chloride **7** (0.5 ml, ~0.20 mmol, prepared from 0.5 mmol acid **16c** dissolved in 1 ml THF) and stirring was continued at -78°C for 30 min. The reaction was quenched with H_2O, warmed up to room temperature by stirring vigorously for 30 min, and diluted with Et_2O. The aequeous layer was extracted with EtOAc (3x) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography yielded **19** (41.9 mg, 61%).

From **21**: To distilled pyridine (1.3 ml, 16.8 mmol) in a high density polyethylene (HDPE) vial at -78°C was added dropwise over 10 minutes a solution of 70% HF•pyridine (0.5 ml, ~17.5 mmol HF, ~4.4 mmol pyridine) to form a nearly equimolar solution of HF•pyridine. This solution was stored at -20°C until needed.

To a solution of the previously prepared C23 OTBS β-diketone **21** (0.025 g, 0.033 mmol) in dry THF (2 ml) in a HDPE vial was rapidly added the HF•pyridine solution prepared above (0.25 ml) in a single portion. The resulting solution was layered with argon, sealed and stirred vigorously for 7 days at room temperature. The vial was unsealed, and the reaction quenched with saturated aqueous $NaHCO_3$ (1 ml). The reaction was diluted with ethyl acetate, the layers separated, and the aqueous phase extracted 3 times with ethyl acetate. The combined organic fractions were pooled, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was subjected to flash chromatography in 30% ethyl acetate/hexanes, which yielded β-diketo alcohol **19** (0.015 g, 0.051 mmol, 70%) as a colorless oil.

Spectroscopic data:

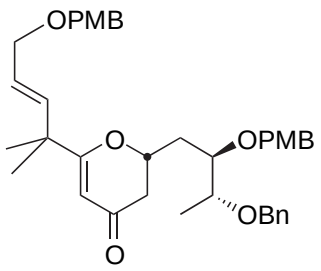
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30-7.35 (m, 4H), 7.25-7.30 (m, 1H) 7.20 (d, *J*=8.4 Hz, 2H), 7.14 (d, *J*=8.4 Hz, 2H), 6.83 (d, *J*=7.8 Hz, 2H), 6.82 (d, *J*=7.8 Hz, 2H), 5.77 (d, *J*=15.8 Hz, 1H), 5.62 (dt, *J*=5.9, 15.8 Hz, 1H), 5.40 (s, 1H), 4.49-4.60 (m, 4H), 4.34-4.37 (m, 2H), 3.91 (d, *J*=5.9 Hz, 2H), 3.79-3.85 (m, 2H), 3.74-3.79 (m, 6H), 3.66-3.74 (m, 1H), 2.32-2.44 (m, 2H), 2.01-2.08 (m, 1H), 1.60-1.68 (m, 1H), 1.22-1.24 (m, 6H), 1.15 (d, *J*=6.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.6, 181.3, 159.3, 159.2, 138.5, 137.9, 137.8, 130.3, 129.6, 129.4, 129.4, 128.4, 128.4, 127.8, 127.6, 127.6, 125.5, 113.9, 113.7, 102.2, 76.2, 76.1, 74.9, 72.9, 72.0, 71.1, 70.3, 55.3, 55.2, 41.8, 41.5, 35.0, 25.3, 25.2, 14.4 ppm.

FTIR (neat): 2970, 1664, 1593, 1513, 1454, 1389, 1334, 1302, 1248, 1174, 1089, 1034, 820, 738, 698 cm^{-1}.

HRMS *m/z* calculated ($C_{30}H_{39}O_7$) 511.2715; observed 511.2696 (PMB group lost).

[α] (589 nM, $CDCl_3$) 0.83% solution, +45.7°



12

To a stirred solution of **19** (1.28 g, 2.02 mmol) in toluene (30 ml) was added *p*-toluene sulfonic acid (0.060 g, 0.0003 mmol) in a single portion followed by addition of 4Å molecular sieves (1.5 g). After stirring at room temperature for 10 hours, the reaction was quenched with pyridine (2.0 ml, 24.7 mmol) and filtered. The resulting solution was concentrated under reduced pressure, then redissolved in dietyhl ether. This was washed with saturated $NaHCO_3$ and dried over $MgSO_4$ before the solvent was removed under reduced pressure. The resulting oil was subjected to flash chromatography in 30% ethyl acetate in hexanes, which was increased to 70% as the product began to elute from the column. This yielded 1.00 g (1.63 mmol, 81%) of **12** as a 1.54:1 mixture of diastereomers at C23 which were separable after a second chromatographic step in which 300 g of silica gel were used per 1 g of the pure diastereomers, and the material was eluted again using 30% ethyl acetate in hexanes.

Spectroscopic data:

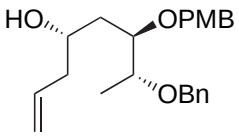
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26-7.34 (m, 5H), 7.20 (d, *J*=8.4 Hz, 2H), 7.14 (d, *J*=8.6 Hz, 2H), 6.80-6.87 (m, 4H), 5.75 (d, *J*=15.8 Hz, 1H), 5.58-5.67 (m, 1H), 5.41 (s, 1H), 4.48-4.61 (m, 4H), 4.33-4.38 (m, 2H), 3.91 (d, *J*=5.9 Hz, 2H), 3.79-3.85 (m, 1H), 3.77 (s, 6H), 3.67-3.74 (m, 1H), 2.35-2.41 (m, 2H), 1.99-2.06 (m, 1H), 1.62-1.67 (m, 1H), 1.23 (br s, 6H), 1.15 (d, *J*=6.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.7, 181.2, 159.3, 159.1, 138.5, 137.8, 130.3, 129.6, 129.5, 129.4, 129.4, 128.4, 128.4, 127.8, 127.7, 127.6, 127.6, 125.5, 113.9, 113.8, 113.7, 102.2, 76.2, 76.1, 74.7, 72.9, 72.0, 71.1, 70.3, 55.3, 41.8, 41.5, 35.0, 31.6, 25.3, 25.2, 24.7, 14.4, 14.1 ppm.

FTIR (neat): 2933, 2885, 1663, 1593, 1513, 1460, 1336, 1302, 1248, 1176, 1090, 1035, 819, 723, 699 cm^{-1}.

HRMS *m/z* calculated ($C_{30}H_{37}O_6$ –4-methoxybenzyl) 493.2590; observed 493.2578.

[α] (589 nm, $CDCl_3$) 0.94% solution, +31.6°



20

In a glove bag, under positive Ar pressure, 0.9834 g (3.11 mmole) methoxy diisopinylborane was weighed into a dried flask. Dry diethyl ether (8.4 ml) was added, and the resulting solution cooled to –78°C. To this solution was added dropwise over 5 minutes a 1M solution of allyl magnesium bromide (2.8 ml, 2.8 mmol), after which the solution was allowed to come to room temperature over 1 hour. A portion (6.2 ml, 2.06 mmole) of the resulting borane reagent was added to a stirred solution of the aldehyde 4 (0.6546 g, 2.0 mmol) in diethyl ether (5 ml) at –78°C over 15 minutes. The reaction was stirred at –78°C for 1 hour, and then allowed to warm to room temperature over 1 hour. The resulting boronate was then cleaved by addition of 10 ml of 15% NaOH and 2 ml 30% H_2O_2. This mixture was stirred for 30 minutes, and the layers were separated. The aqueous layer was then extracted 4 times with diethyl ether. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The resultant oil was subjected to flash chromatography in 15% ethyl acetate/hexanes produced **20** (0.4723 g, 1.28 mmol, 64%) as a clear oil.

Spectroscopic data:

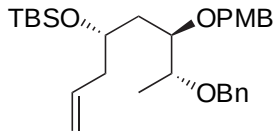
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30-7.33 (m, 4H), 7.26-7.29 (m, 1H), 7.21 (d, *J*=8.7 Hz, 2H), 6.84 (d, *J*=8.7 Hz, 2H), 5.74-5.84 (m, 1H), 5.03-5.10 (m, 2H), 4.45-4.61 (m, 4H), 3.78 (s, 3H), 3.69-3.85 (m, 3H), 2.49 (d, *J*=4.0 Hz, 1H), 2.20 (t, *J*=7.0 Hz, 2H), 1.62-1.65 (m, 2H), 1.15 (d, *J*=6.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 138.5, 134.9, 130.5, 129.8, 129.7, 129.6, 128.41, 128.37, 128.33, 127.69, 127.67, 127.64, 127.58, 117.7, 117.2, 113.9, 113.8,

FTIR (neat): 3442, 3071, 2933, 1641, 1613, 1586, 1514, 1454, 1372, 1302, 1248, 1174, 1074, 1035, 914, 822, 736, 699 cm^{-1}.

HRMS (FAB) *m/z* calculated ($C_{23}H_{30}O_4Na$) 393.2053; observed 393.2042.

[α] (589 nm, $CDCl_3$) 1.10% solution, +18.2°

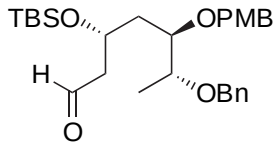


20a

To a stirred solution of **20** (3.39 g, 9.19 mmol) in dry CH_2Cl_2 (80 ml) was added a 60% dispersion of NaH in mineral oil (0.551 g, 13.79 mmol) in a single portion, and the resulting solution was stirred at room temperature for 1 h. To this was added dimethyl aminopyridine (0.061 g, 0.5 mmol), followed by *t*-butyl dimethylsilyl chloride (2.216 g, 14.70 mmol). The solution was then refluxed for 16 h, after which the solution was cooled to room temperature and quenched with 10 ml of a saturated solution of aqueous ammonium chloride. The layers were separated, and the aqueous phase extracted 3 times with ethyl acetate. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The resultant oil was subjected to flash chromatography in 7.5% ethyl acetate/hexanes, yielding the TBS protected allyl alcohol **20a** (3.833 g, 7.90 mmol, 86%) as a clear oil.

Spectroscopic data:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32-7.36 (m, 4H), 7.27-7.30 (m, 1H), 7.22 (d, *J*=8.7 Hz, 2H), 6.86 (d, *J*=8.7 Hz, 2H), 5.75-5.86 (m, 1H), 5.00-5.06 (m, 2H), 4.55-4.59 (m, 3H), 4.45 (d, *J*=11.0 Hz), 3.94-4.00 (m, 1H), 3.80 (s, 3H), 3.68-3.76 (m, 2H), 2.24-2.30 (m, 2H), 1.67 (ddd, *J*=2.2, 9.0, 14.3 Hz), 1.58 (ddd, *J*=3.1, 9.3, 14.3 Hz), 1.15 (d, *J*=6.2 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 138.5, 134.9, 130.5, 129.8, 129.7, 129.6, 128.41, 128.37, 128.33, 127.69, 127.67, 127.64, 127.58, 117.7, 117.2, 113.9, 113.8,
FTIR (neat): 2955, 2929, 2856, 1718, 1613, 1514, 1463, 1370, 1302, 1249, 1172, 1090, 913, 836, 774, 735, 698 cm^{-1}.
HRMS (FAB) *m/z* calculated (C29H44O4NaSi) 507.2929; observed 507.2907.
[α] (589 nm, $CDCl_3$) 0.93% solution, +19.3°

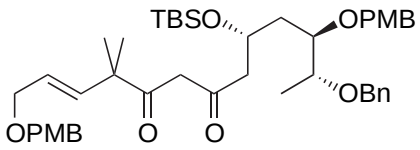


21

To a stirred solution of the previously prepared TBS allyl alcohol **20a** (0.035 g, 0.072 mmol) in 2:1 THF/water (3 ml) was added N-methyl morpholine N-oxide (0.0092 g, 0.079 mmol) in one portion, followed by the rapid addition of a 2.5% solution of osmium tetroxide in isopropanol (0.090 ml, 0.07 mmol), again in one portion. The resultant solution was stirred 6 hours at room temperature before being stopped by the addition of excess solid sodium sulfite. The reaction mixture was then diluted with brine and ethyl acetate. The layers were separated, and the aqueous phase extracted three times with ethyl acetate. The combined organic phases were concentrated under reduced pressure. The resultant oil was redissolved in 3 ml 2:1 tetrahydrofuran/water, to which was added

sodium periodate (0.052 g, 0.243 mmol). The reaction mixture was stirred 6 hours at room temperature before being diluted with water and ethyl acetate. The layers were separated, and the aqueous phase extracted three times with ethyl acetate, and the combined organic phases concentrated under reduced pressure. The resultant yellow oil was subjected to flash chromatography in 10% ethyl acetate/hexanes, and yielded aldehyde **21** (0.0297 g, 0.061 mmol, 85% over 2 steps) as a clear oil.

Spectroscopic data:
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.77 (t, *J*=2.5 Hz, 1H), 7.30-7.36 (m, 4H), 7.25-7.30 (m, 1H), 7.20 (d, *J*=8.6 Hz, 2H), 6.67 (d, *J*=8.4 Hz, 2H), 4.59 (d, *J*=11.8 Hz, 1H), 4.55 (d, *J*=11.0 Hz, 1H), 4.52 (d, *J*=11.8 Hz, 1H), 4.40 (d, *J*=11.0 Hz, 1H), 4.31-4.38 (m, 1H), 3.80 (s, 3H), 3.73-3.79 (m, 1H), 3.66-3.71 (m, 1H), 2.60 (ddd, *J*=2.2, 5.3, 15.9 Hz, 1H), 2.50 (ddd, *J*=2.9, 5.5, 15.8 Hz, 1H) 1.91 (ddd, *J*=2.7, 7.7, 14.3 Hz, 1H), 1.63 (ddd, *J*=4.8, 9.3, 14.3 Hz), 1.16 (d, *J*=6.2 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ 202.3, 159.1, 138.6, 130.57, 129.2, 128.3, 127.5, 113.8, 74.4, 71.7, 71.0, 66.2, 55.3, 51.8, 37.9, 25.8, 18.0, 14.2 ppm.
FTIR (neat): 2929, 2856, 1724, 1612, 1514, 1464, 1388, 1249, 1094, 836, 776 cm^{-1}.
HRMS *m/z* calculated ($C_{28}H_{42}O_5Si$) 486.2802; observed 486.2802.
[α] (589 nm, $CDCl_3$) 1.34% solution, +19.2°



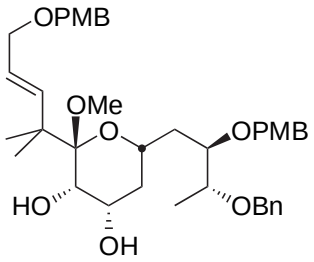
21a

To a stirred solution of diisopropyl amine (0.352 ml, 2.51 mmol) in dry THF (25 ml) at -78°C was added dropwise a 2.5M solution of *n*BuLi in hexanes (0.956 ml, 2.39 mmol). The solution was stirred for 30 minutes at 0°C and then cooled to –78°C. A solution of methyl ketone **10** (0.592 g, 2.26 mmol) in dry THF (5 ml) was cannulated slowly into the reaction mixture over 10 minutes. The resulting solution was stirred at –78°C for 30 minutes, warmed to room temperature for 2 minutes, then recooled to -78°C, after which a solution of aldehyde **21** (1.0 g, 2.05 mmol) in dry THF (3 ml) was slowly cannulated into the reaction mixture over 10 minutes. This was stirred at –78°C for 15 minutes, then quenched with a saturated solution of aqueous ammonium chloride (25 ml). The reaction was then diluted with ethyl acetate, and the layers separated. The aqueous phase was extracted 3 times with ethyl acetate, and the combined organic phases dried with $MgSO_4$ and concentrated under reduced pressure. The resulting oil was subjected to flash chromatography in 10% ethyl acetate in hexanes, which was increased to 20% as the product began to elute from the column. This yielded 1.48 g (1.97 mmol, 96%) of an inconsequential mixture of diastereomers which were carried through to the next reaction.

To a stirred solution of the diastereomeric mixture of β-keto alcohols (0.1103 g, 0.147 mmol) in dry CH_2Cl_2 was added N-methyl morpholine N-oxide (0.1418 g, 1.207 mmol) and approximately 0.1 g powdered 4Å molecular sieves. Tetrapropyl ammonium

perruthenate (0.0131 g, 0.037 mmol) was added and the mixture stirred for 30 minutes. The reaction mixture was then filtered through a short plug of silica with copious quantities of ethyl acetate. The resulting solution was concentrated under reduced pressure and subjected to flash chromatography using 15% ethyl acetate in hexanes. This yielded 0.0513 g (0.069 mmol, 47%) of the desired β-diketone **19**.

Spectroscopic data:
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29-7.31 (m, 4H), 7.25-7.27 (m, 1H), 7.24 (d, *J*=8.8 Hz, 2H), 7.20 (d, *J*=8.6 Hz, 2H), 6.85 (d, *J*=8.8 Hz, 2H), 6.83 (d, *J*=8.6 Hz, 2H), 5.78 (d, *J*=15.8 Hz, 1H), 5.63 (dt, *J*=6.0, 15.8 Hz, 1H), 5.57 (s, 1H), 4.48-4.57 (m, 4H), 4.40-4.42 (m, 2H), 4.23-4.28 (m, 1H), 3.96 (dd, *J*=1.3, 6.0 Hz, 2H), 3.77 (s, 6H), 3.67-3.72 (m, 1H), 3.63-3.67 (m, 1H), 2.47 (dd, *J*=5.1, 13.9 Hz, 1H), 2.37 (dd, *J*=7.1, 13.9 Hz, 1H), 1.78 (ddd, *J*=2.6, 7.0, 14.3 Hz, 1H), 1.61 (ddd, *J*=5.1, 9.2, 14.3 Hz, 1H), 1.22 (s, 6H), 1.12 (d, *J*=6.2 Hz, 3H), 0.83 (s, 9H), 0.02 (s, 3H), -0.03 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ 189.3, 159.2, 159.1, 138.7, 138.1, 130.7, 130.3, 129.5, 129.2, 128.3, 127.5, 127.4, 125.5, 113.8, 98.1, 77.6, 74.8, 71.8, 71.7, 71.0, 68.1, 55.3, 47.0, 45.4, 38.1, 25.9, 25.8, 24.6, 18.0, 14.4, -4.5 ppm.
FTIR (neat): 2931, 2855, 1812, 1612, 1514, 1464, 1361, 1302, 1248, 1173, 1094, 1036, 845, 776 cm^{-1}.
HRMS (FAB) *m/z* calculated ($C_{44}H_{62}O_8NaSi$) 769.4137; observed 769.4112.
[α] (589 nm, $CDCl_3$) 1.76% solution, -1.15°



22

To a solution of pyranone **12** (0.205 g, 0.333 mmol) and cerium chloride heptahydrate (0.030 g, 0.082 mmol) in 5.5 ml methanol was added solid $NaBH_4$ (0.012 g, 0.33 mmol) in a single portion at -20°C. The reaction mixture was stirred for 1 hour at -20°C and monitored by tlc. A second portion of $NaBH_4$ (0.012 g, 0.33 mmol) was added during this period when the reaction appeared stalled. The reaction was then quenched with 20 ml saturated aqueous NaCl, and the mixture brought to room temperature, filtered through a pad of Celite® and the layers separated. The separated aqueous layer was extracted four times with ethyl acetate, and the combined organics were dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude allylic alcohol. This moderately stable oil was reacted further without purification.
The crude allylic alcohol was dissolved in 6 ml CH_2Cl_2/MeOH (2:1) and cooled to 0°C before being treated with solid $NaHCO_3$ (0.042 g, 0.5 mmol). Purified *m*-chloroperoxybenzoic acid (0.046 g, 0.370 mmol) was added in a single portion and the reaction mixture was stirred for 30 minutes, then warmed to room temperature over a

period of 15 minutes. The reaction was quenched with triethylamine (4.0 ml), stirred well for 20 minutes, diluted with 40 ml diethyl ether, and filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure and the resulting oil purified using flash chromatography using (EtOAc/hexane 1/1) to give diol **22** (0.158 g, 0.238 mmol, 71%) as a colorless oil.

Spectroscopic data:

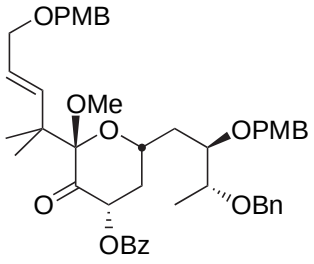
^{1}H NMR (500 MHz, $CDCl_3$) δ (/ppm) 1.15-1.24 (10H, m), 1.48 (1H, q, *J* = 12.3 Hz), 1.55-1.67 (2H, m), 1.86 (1H, dd, *J* = 11.2, 13.2 Hz), 2.04 (H, d, *J* = 4.6 Hz), 2.11 (1H, d, *J* = 10.1 Hz), 3.25 (3H, s), 3.73-3.83 (3H, m), 3.76 (6H, s), 3.86-3.98 (4H, m), 4.40 (3H, m), 4.59 (3H, m), 5.60 (1H, dt, *J* = 6.2, 16.1 Hz), 6.17 (1H, d, *J* = 15.9 Hz), 6.81 (2H, d, *J* = 8.6 Hz), 6.83 (2H, d, *J* = 8.4 Hz), 7.14 (2H, d, *J* = 8.6 Hz), 7.22 (2H, d, *J* = 8.4 Hz), 7.29-7.35 (5H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ (/ppm) 14.4, 22.3, 24.9, 34.2, 36.1, 45.7, 51.8, 55.2, 66.7, 67.1, 70.3, 70.8, 71.1, 71.8, 72.0, 74.7, 102.9, 123.0, 127.5, 128.4, 129.2, 129.4, 130.3, 130.6, 138.7, 142.1, 159.1.

FTIR (neat): 2970, 1664, 1593, 1513, 1454, 1389, 1334, 1302, 1248, 1174, 1089, 1034, 820, 738, 898 cm^{-1}.

HRMS (FAB) *m/z* calculated: ($C_{39}H_{52}O_9$) 664.360;
($C_{30}H_{39}O_7$; M^+ -4-methoxybenzyl, -MeOH) 511.269; observed (M): 511.271;
($C_{38}H_{46}O_7$; M^+ -H_2O, -MeOH) 614.324; observed (M): 614.325.

$[\alpha]_D$ (589 nm, $CDCl_3$, c = 0.23) = +9.7°.



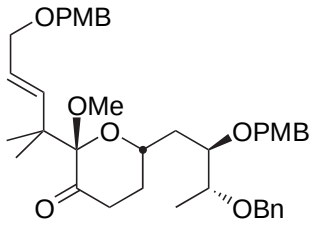
22a

A solution of diol **22** (118 mg, 0.178 mmol) and 4-dimethylaminopyridine (77 mg, 0.62 mmol) in CH_2Cl_2 (3.2 ml) was cooled to -10°C and treated with benzoyl chloride (27 µl, 0.23 mmol) dropwise via syringe. The resulting mixture was stirred at -10°C for 30 minutes, quenched with saturated $NaHCO_3$ and diluted with EtOAc (20 ml). The organic layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford a crude mixture of C21 monobenzoate and 4-dimethylaminopyridine as a colorless paste, which was filtered over a plug of silica gel (EtOAc/hexane 1/2).

The filtrate was evaporated and taken up in 8 ml CH_2Cl_2 and treated with solid 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin periodinane, 113 mg, 0.267 mmol) at room temperature. The solution was stirred for 4 hours at room temperature after which a second portion (113 mg, 0.267 mmol) of DMP was added. The opaque white mixture was stirred for another 1.5 hours and quenched with 4 ml saturated $NaHCO_3$ / $Na_2S_2O_3$. The layers were separated and the aquous phase was extracted with

CH_2Cl_2 (2 x). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to provide a colorless semisolid. Flash chromatography on silica gel (EtOAc/hexane 1/3) gave the desired keto-pyranone **22a** (121 mg, 89% from **22**) as a colorless oil.

Spectroscopic data:
^{1}H NMR (300 MHz, $CDCl_3$) δ (/ppm) 1.19 (3H, d, *J* = 6.3 Hz, 27-H), 1.24, 1.25 (6H, s, s, CH_3), 1.68 (1H, m), 1.87 (1H, m), 2.13 (1H, m), 2.42 (1H, dd), 2.42 (1H, dd, *J* = 10.1 Hz), 3.47 (3H, s, OMe), 3.69-3.97 (4H, m), 3.77, 3.80 (6H, s, s, OMe), 4.38-4.62 (6H, m), 4.46 (1H, d, *J* = 11.2 Hz), 5.64 (1H, dt, 16-H), (1H, dd, *J* = 6.3, 12.9 Hz, 21-H), 6.23 (1H, d, *J* = 15.9 Hz), 6.83 (2H, d, *J* = 8.8 Hz), 6.86 (2H, d, *J* = 8.8 Hz), 7.21-7.60 (9H, m, aromatic), 8.08 (2H, d, *J* = 8.3 Hz).
^{13}C NMR (75 MHz, $CDCl_3$) δ (/ppm) 14.5, 23.0, 23.5, 27.7, 35.3, 40.5, 44.1, 53.6, 55.3, 60.4, 65.2, 71.0, 71.4, 72.7, 73.0, 75.0, 76.9, 103.2, 113.7, 124.4, 127.5, 128.4, 129.3, 129.4, 129.5, 129.9, 130.4, 130.6, 133.3, 138.6, 140.2, 159.0, 159.2, 165.5, 198.1.
FTIR (neat): 2935, 1753, 1724, 1612, 1586, 1514, 1452, 1382, 1361, 1249, 1175, 1112, 1069, 1036, 822, 738, 711 cm^{-1}.
MS (ESI Q/MS) *m/z* calculated: ($C_{46}H_{54}O_9$) 766.37;
($C_{38}H_{46}O_9Na$, M^+ -4-methoxybenzyl, +Na): 669.3; observed: 669.3.
$[\alpha]_D^{25.9}$ (589 nm, $CDCl_3$, c = 0.79) = +25.5°.

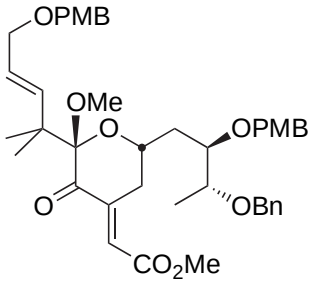


23

A stirred solution of the above keto-pyranone (434 mg, 0.567 mmol) in 12 ml THF / MeOH (3:1) was titrated with SmI_2 (0.1 M solution in THF, 17 ml, 1.70 mmol) at -78°C until an olive green color persisted. The reaction mixture was then quenched with 5 ml saturated $NaHCO_3$, warmed to room temperature and diluted with EtOAc (200 ml). The organic layer was washed with saturated $NaHCO_3$, H_2O and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography on silica gel (20% EtOAc / hexanes) afforded **23** (319 mg, 87%) as a light yellow oil.

Spectroscopic data:
^{1}H NMR (300 MHz, $CDCl_3$) δ (/ppm) 1.13-1.21 (9H, m, CH_3, 27-H), 1.57-1.95 (4H, m), 2.44 (2H, m), 3.26 (3H, s, OMe), 3.79 (7H, s, m, OMe), 3.96 (2H, d, *J* = 6.0 Hz), 3.94 (1H, m), 4.14 (1H, m), 4.41-4.66 (4H, m), 4.41 (1H, d, *J* = 10.6 Hz), 4.59 (1H, d, *J* = 10.6 Hz), 5.55 (1H, dt, 16-H, *J* = 15.9, 6.1 Hz), 6.07 (1H, d, *J* = 15.9 Hz), 6.41 (2H, d, *J* = 8.8 Hz), 6.86 (2H, d, *J* = 8.4 Hz), 7.16-7.34 (9H, m, aromatic).
^{13}C NMR (75 MHz, $CDCl_3$) δ (/ppm) 14.2, 22.3, 22.5, 30.1, 36.0, 37.4, 44.2, 52.2, 69.4, 70.8, 71.1, 72.0, 74.4, 76.6, 103.7, 113.7, 113.8, 124.6, 127.6, 128.4, 129.3, 129.4, 129.8, 130.5, 130.7, 138.7, 139.6, 159.3, 207.3.

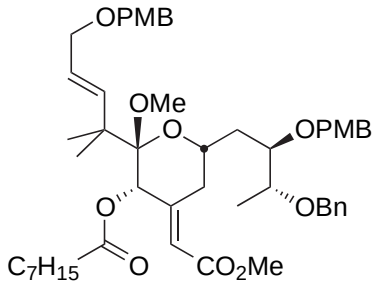
FTIR (neat): 2926, 2850, 1725, 1611, 1587, 1514, 1455, 1382, 1361, 1302, 1248, 1173, 1111, 1078, 1040, 983, 820, 738, 699 cm^{-1}.
HRMS (FAB) *m/z* calculated: ($C_{39}H_{50}O_8$) 646.382;
($C_{38}H_{46}O_7$; M^+ - MeOH) 614.324; observed (M): 614.326.
$[\alpha]_D^{26.4}$ (589 nm, $CDCl_3$, c = 0.51) = +23.3°.



24

To a stirred solution of diisopropylamine (300 µl, 2.14 mmol) in THF (3.2 ml) was added *n*-butyllithium (1.25 ml, 1.6 M in hexanes, 2.00 mmol) dropwise at -78°C. The mixture was warmed to 0°C and stirred for 30 min, then cooled again to -78°C, and a solution of ketone **23** (319 mg, 0.494 mmol) in 6.8 ml THF was added in a single portion. The solution was stirred for 30 minutes and treated with a solution of freshly distilled $OHCCO_2Me$ (88 mg, 0.74 mmol) in 5 ml THF, kept at -78°C for 30 minutes and quenched with 3 ml saturated NH_4Cl. The reaction mixture was brought to room temperature and diluted with 200 ml EtOAc. The organic layer was washed with H_2O (2x) and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was chromatographed on silica gel (EtOAc/hexanes 35/65) to afford the aldol product (319 mg, 88%) as an inconsequential mixture of diastereomers.
The isolated aldol product (303 mg, 0.412 mmol) and Et_3N (340 µl, 2.50 mmol) were dissolved in anhydrous CH_2Cl_2 (15 ml) and cooled to -10°C. Methanesulfonylchloride (97 µl, 1.25 mmol) was added via syringe and the solution was stirred at -10°C for 30 minutes and warmed to room temperature. 5 ml saturated $NaHCO_3$ were added and the reaction mixture was diluted with 100 ml EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was immediately dissolved in THF (20 ml) and treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU - 75 µl, 0.5 mmol) dropwise at room temperature. The resulting bright yellow solution was stirred at room temperature for 20 minutes, treated with saturated NH_4Cl and diluted with 150 ml EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford an orange residue which was chromatographed on silica gel (20% EtOAc / hexanes) to afford exocyclic methacrylate **24** (239 mg, 81% - unseparable mixture of *E*/*Z* isomers, ratio *E*/*Z* = 7:1) as a yellow oil.

Spectroscopic data:
^{1}H NMR (300 MHz, $CDCl_3$) δ (/ppm) 1.00-1.28 (9H, m, CH_3, 27-H), 1.74 (1H, m), 1.98 (1H, m), 2.83 (1H, m), 3.23 (3H, s, OMe), 3.71 (3H, s OMe), 4.74-3.88 (1H, m), 3.78 (3H, s OMe), 3.79 (3H, s OMe), 3.89 (2H, d, *J* = 5.9 Hz), 3.95 (1H, m), 4.14 (1H, m), 4.36 (3H, m), 4.58 (3H, m), 5.46 (1H, dt, *J* = 15.9, 6.1 Hz, 16-H), 5.85 (1H, d, *J* = 15.9 Hz), 6.55 (1H, s; minor *Z*-isomer: 6.45, s; *E*/*Z* = 7:1), 6.82 (2H, d, *J* = 8.8 Hz), 6.85 (2H, d, *J* = 8.5 Hz), 7.12-7.35 (9H, m, aromatic).
^{13}C NMR (75 MHz, $CDCl_3$) δ (/ppm) 14.2, 22.0, 22.2, 35.9, 44.8, 51.7, 52.1, 55.2, 69.3, 70.7, 71.0, 71.5, 716, 74.2, 76.6, 104.5, 113.7, 122.8, 125.5, 127.5, 127.9, 128.3, 129.0, 129.4, 129.8, 130.4, 130.5, 138.1, 138.5, 147.9, 159.1, 166.0, 197.4.
FTIR (neat): 2937, 2833, 1721, 1700, 1611, 1579, 1511, 1459, 1438, 1381, 1360, 1291, 1250, 1208, 1177, 1109, 1072, 1030, 983, 941, 821, 737, 696 cm^{-1}.
MS (ESI Q/MS) *m/z* calculated: ($C_{42}H_{52}O_{10}$) 716.36;
($C_{34}H_{44}O_9Na$, M^+ -4-methoxybenzyl, +Na): 619.3; observed: 619.1.
$[\alpha]_D^{24.9}$ (589 nm, $CDCl_3$, c = 0.93) = -31.2°.

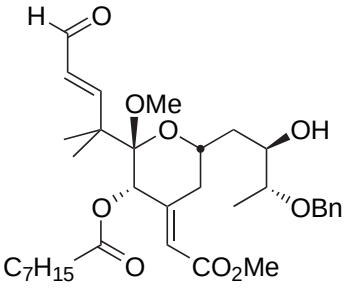


25

To a solution of enone **24** (205 mg, 0.286 mmol) and cerium chloride heptahydrate (52 mg, 0.15 mmol) in 11 ml methanol was added solid $NaBH_4$ (21 mg, 0.57 mmol) in a single portion at -30°C. Rapid gas evolution subsided after 3 minutes. After an additional 30 minutes at - 30°C, the reaction mixture was poured directly onto a silica gel column and the product quickly eluted with EtOAc / hexanes (3/1) to afford the alcohol as colorless oil.
Octanoic acid (93 mg, 0.64 mmol) and Et_3N (117 µl, 0.88 mmol) were dissolved in 8 ml toluene and treated with 2,4,6-trichlorobenzoylchloride (92 µl, 0.59 mmol) dropwise at room temperature. After 2.5 hours at room temperature, a toluene solution (5 ml) of freshly prepared alcohol was added gradually via syringe and stirring was continued for 1 h. The reaction mixture was quenched with 10 ml saturated $NaHCO_3$, diluted with EtOAc and washed successively with saturated NH_4Cl and brine. The organics were dried over Na_2SO_4, the solvent was removed *in vacuo*, and the residue was chromatographed on silica gel (EtOAc/hexane 1/3) to provide octanoate **25** as an colorless oil (208 mg, 86% from **24**).

Spectroscopic data:
^{1}H NMR (300 MHz, $CDCl_3$) δ (/ppm) 0.79-1.21, 1.54 (24H, m), 1.81 (1H, m), 2.41 (1H, t, *J* = 14.9 Hz), 2.28 (1H, t, *J* = 7.6 Hz), 3.18 (3H, s, OMe), 3.61 (3H, s OMe), 3.71 (3H, s

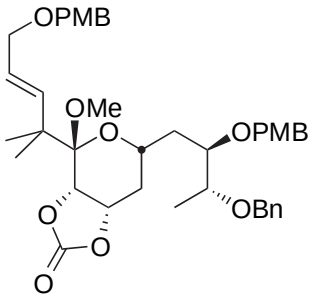
OMe), 3.72 (3H, s OMe), 3.73 (1H, m), 3.87 (2H, d, *J* = 6.1 Hz), 3.88 (1H, m), 3.97 (1H, m), 4.21-4.57 (6H, m), 5.53 (1H, dt, *J* = 16.1, 6.1 Hz, 16-H), 5.84 (1H, s), 6.08 (1H, d, *J* = 16.1 Hz), 6.75 (2H, d, *J* = 8.8 Hz), 6.78 (2H, d, *J* = 8.8 Hz), 7.07-7.30 (10H, m, aromatic + 1H).
^{13}C NMR (75 MHz, $CDCl_3$) δ (/ppm) 13.8, 14.2, 15.0, 22.4, 22.8, 23.9, 24.5, 28.7, 28.8, 31.4, 32.4, 33.5, 36.1, 45.7, 50.8, 50.9, 55.0, 65.6, 67.8, 70.5, 70.9, 71.6, 71.7, 73.2, 74.4, 76.2, 76.4, 102.6, 113.5, 114.9, 123.6, 127.3, 127.7, 128.1, 129.0, 129.1, 129.2, 129.5, 130.1, 130.4, 138.5, 141.2, 156.3, 158.9, 166.6.
FTIR (neat): 3418, 2933, 1715, 1655, 1612, 1586, 1514, 1456, 1438, 1380, 1302, 1249, 1174, 1159, 1099, 1035, 821, 738, 699 cm^{-1}.
MS (ESI Q/MS) *m/z* calculated: ($C_{50}H_{68}O_{11}$) 845.48;
($C_{42}H_{60}O_{10}Na$, M^+ -4-methoxybenzyl, +Na): 747.4; observed: 747.3.
$[\alpha]_D^{23.3}$ (589 nm, $CDCl_3$, c = 0.93) = +6.30°.



2

To a solution of **25** (2.0 mg, 0.0024 mmol) in 1 mL 1% aqueous CH_2Cl_2 was added solid 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 1.2 mg, 0.0053 mmol) at 0 °C. The reaction mixture was stirred for 30 minutes, then pipetted directly onto a plug of silica gel. The product was eluted with EtOAc/hexane (1/4) and the solvent was removed *in vacuo* to provide the crude diol (1.1 mg). This material was dissolved in anhydrous CH_2Cl_2 and treated with manganese(IV) oxide (0.4 mg, 0.0046 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and then pipetted directly onto a plug of silica gel. The product was eluted with EtOAc/hexane (1/3) and the solvent was removed *in vacuo*. Crude aldehyde **2** (0.64 mg, 42%) was obtained as a colorless oil. The ^{1}H NMR data of **2** are good in agreement with the published data (Wender et al. *J. Am. Chem. Soc.* **1998**, *120*, 4534. – Supplemental Material).

Spectroscopic data:
^{1}H NMR (300 MHz, $CDCl_3$) δ (/ppm) 0.87 (3H, t, *J* = 6.7 Hz, Me), 1.16 (3H, s, Me), 1.18 (3H, s, Me), 1.30 (10H, m), 1.54 (2H, m), 1.74 (2H, m), 2.13 (2H, m), 2.35 (1H, m), 2.59 (1H, d, *J* = 3.8 Hz), 3.43 (3H, s, OCH_3), 3.44 (1H, m), 3.70 (3H, s, OCH_3), 3.82 (1H, s), 4.25 (1H, m), 4.44 (1H, d, *J* = 10.8 Hz), 4.70 (1H, d, *J* = 11.2), 5.48 (1H, s), 5.88 (1H, s), 5.91 (1H, dd, *J* = 15.7, 7.3 Hz), 7.29 (1H, d, *J* = 15.7 Hz) 7.37 (5H, m, aromatic), 9.52 (1H, d, *J* = 7.2 Hz).

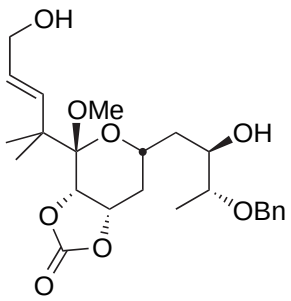


26

To a stirred solution of diol **22** (0.1974 g, 0.297 mmol) and pyridine (0.145 ml, 1.79 mmol) in dry CH_2Cl_2 at 0°C was added triphosgene (0.125 g, 0.421 mmol) dissolved in dry CH_2Cl_2 (1 ml) dropwise over 5 minutes. The resulting solution was stirred for 30 minutes at 0°C and then quenched with a saturated aqueous solution of $NaHCO_3$ (0.5 ml). This was diluted with CH_2Cl_2, and the layers separated. The aqueous phase was extracted three times with CH_2Cl_2, and the combined organic fractions dried over Na_2SO_4 and concentrated under reduced pressure. The resultant oil was purified using flash chromatography using 30% ethyl acetate in hexanes to give **26** (0.1906 g, 0.276 mmol, 93%) as a colorless oil.

Spectroscopic data:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (d, *J*=4.4 Hz, 4H), 7.25-7.30 (m, 1H), 7.21 (d, *J*=8.6 Hz, 2H), 7.10 (d, *J*=8.6 Hz, 2H), 6.81 (d, *J*=8.6 Hz, 2H), 6.80 (d, *J*=8.6 Hz, 2H), 6.02 (d, *J*=15.9 Hz, 1H), 5.61 (dt, *J*=6.1, 15.8 Hz, 1H), 4.73 (dt, *J*=6.2, 9.9 Hz, 1H), 4.59 (d, *J*=11.7 Hz, 1H), 4.54 (d, *J*=10.8 Hz, 1H), 4.53 (d, *J*=11.7 Hz, 1H), 4.40, (d, *J*=1.3 Hz, 2H), 4.38 (d, *J*=6.0 Hz, 1H), 4.26 (d, *J*=10.8 Hz, 1H), 3.96 (dd, *J*=1.3, 6.0 Hz, 2H), 3.87-3.92 (m, 1H), 3.78-3.82 (m, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.68-3.75 (m, 1H), 3.16 (s, 3H), 2.05 (ddd, *J*=2.6, 6.4, 13.6, 1H), 1.90 (ddd, *J*=2.2, 9.7, 14.6 Hz, 1H), 1.56-1.64 (m, 1h), 1.43 (dt, *J*=10.5, 13.4 Hz, 1H), 1.21 (s, 3H), 1.19 (s, 3H), 1.16 (d, *J*=6.4 Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 159.1, 154.2, 139.5, 138.5, 130.4, 130.4, 129.4, 129.2, 128.4, 127.6, 127.5, 124.2, 113.8, 113.7, 101.0, 76.1, 74.4, 74.2, 73.6, 71.8, 71.7, 71.1, 71.0, 74.1, 55.3, 55.2, 51.9, 45.5, 41.0, 35.8, 32.1, 24.3, 22.5, 14.1 ppm.
FTIR (neat): 2936, 1810, 1612, 1513, 1465, 1360, 1248, 1173, 1078, 1031, 820 cm^{-1}.
HRMS (FAB) *m/z* calculated ($C_{40}H_{50}O_{10}Na$) 713.3309; observed 713.3302.
[α] (589 nm, $CDCl_3$) 1.20% solution, +34.0°



26a

To a stirred solution of **26** (0.0467 g, 0.068 mmol) in 1% aqueous CH_2Cl_2 (5 ml) was added solid dichlorodicyanoquinone (0.0397 g, 0.175 mmol) in a single portion. The resulting green solution was stirred vigorously for 2 hours, during which time the the solution became orange. The reaction was stopped by filtering the solution through a pad of silica gel using 80% ethyl acetate in hexanes to wash the silica thoroughly. The resulting light orange solution was concentrated under reduced pressure and redissolved in 50% ethyl acetate in hexanes. This solution was washed 3x with brine, and the combined aqueous layers back extracted 2x with 50% ethyl acetate in hexanes. All of the organic layers were combined, dried with Na_2SO_4 and concentrated under reduced pressure. The resultant oil was subjected to flash chromatography, eluting with 50% to 80% ethyl acetate in hexanes to give the desired diol **26a** (0.0203 g, 0.045 mmol, 66%) as a colorless oil.

Spectroscopic data:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28-7.37 (m, 5H), 5.97 (d, *J*=16.0 Hz, 1H), 5.62 (dt, *J*=6.0, 15.9 Hz, 1H), 4.80 (dt, *J*=6.2, 10.1 Hz, 1H), 4.68 (d, *J*=11.5 Hz, 1H), 4.41 (d, *J*=11.4 Hz, 1H), 4.39 (d, *J*=6.0 Hz, 1H), 4.07-4.13 (m, 2H), 3.86 (t, *J*=10.3 Hz, 1H), 3.76-3.83 (m, 1H), 3.36 (t, *J*=6.6 Hz, 1H), 3.31 (s, 3H), 2.71 (d, *J*=4.0 Hz, 1H), 2.06 (ddd, *J*=2.2, 6.4, 13.4 Hz, 1H), 1.53-1.71 (m, 4H), 1.45 (q, *J*=11.0 Hz, 1H), 1.23 (d, *J*=6.0 Hz, 3H), 1.19 (s, 3H), 1.17 (s, 3H) ppm.

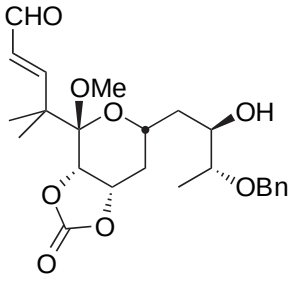
^{13}C NMR (125 MHz, $CDCl_3$):

δ 154.3, 138.6, 137.9, 128.5, 127.9, 126.3, 101.0, 78.4, 74.6, 73.7, 71.1, 70.8, 74.1, 73.7, 52.1, 45.5, 39.3, 32.0, 24.0, 22.7, 15.5 ppm.

FTIR (neat): 3417, 2973, 1806, 1654, 1454, 1377, 1330, 1174, 1077, 1043, 982, 825, 776, 739, 699 cm^{-1}.

HRMS (FAB) *m/z* calculated ($C_{24}H_{34}O_8Na$) 473.2156; observed 473.2151.

[α] (589 nm, $CDCl_3$) 0.80% solution, +65.4°

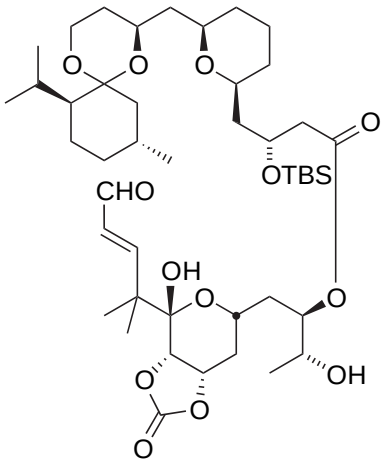


27

To a stirred solution of the previously prepared diol **26a** (0.0200 g, 0.044 mmol) in dry CH_2Cl_2 (4 ml) was rapidly added manganese dioxide (0.0869 g, 1.0 mmol) in a single portion. The manganese dioxide had been previously activated by heating to 180°C for 8 hours followed by application of high vacuum for 12 hours. The resulting suspension was stirred vigorously for 3 hours after which the reaction was stopped by filtering the mixture through a pad of Celite washing thoroughly with CH_2Cl_2. The resulting liquid was concentrated under reduced pressure and subjected to flash chromatography, eluting

with 50% to 70% ethyl acetate in hexanes to give the desired aldehyde **27** (0.0137 g, 0.031 mmol, 70%, 80% based on recovered diol) as a colorless oil.

Spectroscopic data:
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.53 (d, *J*=7.7 Hz, 1H), 7.27-7.37 (m, 4H), 7.17 (d, *J*=16.1 Hz, 1H), 6.08 (dd, *J*=7.7, 16.1 Hz, 1H), 4.83 (dt, *J*=6.2, 10.3 Hz, 1H), 4.69 (d, *J*=11.4 Hz, 1H), 4.39-4.43 (m, 2H), 3.92 (t, *J*=10.6 Hz, 1H), 3.72-3.78 (m, 1H), 3.36 (t, *J*=6.2 Hz, 1H), 3.32 (s, 3H), 2.66 (d, *J*=3.1 Hz, 1H), 2.11 (ddd, *J*=2.2, 6.6, 13.4 Hz, 1H), 1.69 (t, *J*=13.7 Hz, 1H), 1.54-1.61 (m, 2H), 1.46 (q, *J*=11.0, 1H), 1.27 (br s, 6H), 1.24 (d, *J*=6.0, 3H) ppm.
^{13}C NMR (125 MHz, $CDCl_3$): δ 194.5, 163.9, 153.7, 137.8, 129.4, 128.6, 128.0, 128.0, 100.6, 78.4, 74.2, 73.4, 71.1, 70.8, 64.0, 51.8, 47.0, 39.3, 32.2, 23.1, 22.5, 15.6 ppm.
FTIR (neat): 3490, 2975, 1810, 1685, 1454, 1378, 1330, 1171, 1109, 1077, 1043, 824, 739, 699 cm^{-1}.
HRMS (FAB) *m/z* calculated ($C_{24}H_{32}O_8Na$) 471.1992; observed 471.1995.
[α] (589 nm, $CDCl_3$) 1.39% solution, +40.3°



29

To a stirred solution of **27** (0.0073 g, 0.016 mmol) in 10% H_2O in acetonitrile (1 ml) in a polyethylene vial was added 48% aqueous HF (0.250 ml, 6.0 mmol), and the resulting solution heated to 45°C in an oil bath. The reaction was stirred for 3 hours, then was stopped through addition of a saturated aqueous solution of $NaHCO_3$ (2 ml). The layers were separated and the aqueous phase extracted 3 times with ethyl acetate. The combined organic fractions were dried with solid Na_2SO_4, filtered and concentrated under reduced pressure. The resulting oil was subjected to flash chromatography, eluting with 70% ethyl acetate in hexanes to give the desired ketal **28** (0.0055 g, 0.013 mmol, 79%) as a colorless oil.

To a stirred solution of **13** (0.0103 g, 0.020 mmol) in dry toluene (1 ml) was added distilled triethylamine (0.008 ml, 0.058 mmol), followed by 2,4,6-trichlorobenzoyl chloride (0.005 ml, 0.024 mmol). The resulting solution was stirred at room temperature for 1 hour, at which point, a solution of the previously prepared ketal (0.0079 g, 0.018

mmol) in dry toluene (1 ml) was added. Solid dimethylamino pyridine (0.0164 g, 0.134 mmol) was added to the reaction mixture and it was stirred for 1 hour at room temperature. The reaction mixture liquid was transferred directly onto a silica gel column, which had been pre-equilibrated with 20% ethyl acetates in hexane. The product was eluted with 30% ethyl acetate in hexanes, and the product containing fractions concentrated under reduced pressure to give **29** (0.0106 g, 0.011 mmol, 62%) as a colorless oil.

Spectroscopic data:

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.47 (d, 1H), 7.25-7.35 (m, 5H), 7.18 (d, 1H), 6.17 (dd, 1H), 5.23 (m, 1H), 4.82 (m, 1H), 4.59 (d, 1H), 4.45 (d, 1H), 4.40 (d, 1H), 4.23 (m, 1H), 4.10 (q, 1H), 4.03 (br t, 1H), 3.88 (m, 1H), 3.79 (dd, 1H), 3.67 (m, 1H), 3.55 (m, 1H), 3.32-3.45 (m, 3H), 2.63 (br d, 1H), 2.45-2.55 (m, 2H), 2.33-2.41 (m, 1H), 2.01-2.05 (m, 1H), 2.01 (s, 1H), 1.09-1.93 (m), 0.97 (d, 1H), 0.80-0.90 (m, 6H), 0.05 (s, 3H), 0.02 (s, 3H), -0.02 (s, 9H) ppm.

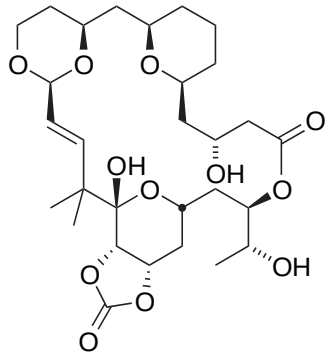
^{13}C NMR (125 MHz, $CDCl_3$):

δ 154.3, 138.6, 137.9, 128.5, 127.9, 126.3, 101.0, 78.4, 74.6, 73.7, 71.1, 70.8, 74.1, 73.7, 52.1, 45.5, 39.3, 32.0, 24.0, 22.7, 15.5 ppm.

FTIR (neat): 3466, 2938, 2864, 1816, 1719, 1690, 1458, 1379, 1309, 1254, 1111, 980, 836, 777, 739, 700 cm^{-1}.

HRMS (FAB) *m/z* calculated ($C_{52}H_{82}O_{13}NaSi$) 965.5391; observed 965.5422.

[α] (589 nm, $CDCl_3$) 0.37% solution, +30.5°



30

To a stirred solution of **29** (0.0070 g, 0.007 mmol) in dry THF (1 ml) in a polyethylene vial was rapidly added a single portion of HF•pyridine (0.25 ml) prepared in a fashion identical to that used for **19**. The resulting solution was stirred for 31 hours before being stopped by addition of a saturated aqueous solution of Na_2HCO_3 (2 ml). The reaction was diluted with ethyl acetate and the layers separated. The aqueous phase was extracted 3 times with ethyl acetate and the combined organic fractions dried with Na_2SO_4 and concentrated under reduced pressure. The resulting oil was subjected to flash chromatography, eluting with 40% ethyl acetate in hexanes to give the C3 deprotected material (0.0054 g, 0.0065 mmol, 88% as a colorless oil.

The oil resulting from the above deprotection (0.0076 g, 0.009 mmol) was dissolved in dry CH_2Cl_2 (1 ml), and 4 beads of 4Å molecular sieves were added, followed by the addition of approximately 30 beads of Amberlyst-15 ion exchange resin. The resulting mixture was stirred 12 hours, and the solids filtered off, washing thoroughly with CH_2Cl_2, and the product containing solution concentrated under reduced pressure. The resulting oil was subjected to flash chromatography, eluting with 40% ethyl acetate in hexanes to give the C26 benzylated analog (0.0043 g, 0.006 mmol, 71%) as a colorless oil.

To a stirred solution of the C26 benzylated analog (0.0021 g, 0.003 mmol) in HPLC grade ethyl acetate (1 ml) was added solid $Pd(OH)_2$. The resulting suspension was stirred vigorously under a hydrogen atmosphere for 1 hour. The reaction was stopped by filtering the reaction mixture through a plug of Celite, washing extensively with ethyl acetate. The resultant solution was concentrated under reduced pressure and the resulting oil was subjected to flash chromatography, eluting with 80% ethyl acetate in hexanes to give **30** (0.0016 g, 0.0027 mmol, 88%) as an amorphous white solid.

Spectroscopic data:
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.94 (d, *J*=16.1 Hz, 1H), 5.48 (s, 1H), 5.43 (dd, *J*=7.5, 16.1 Hz, 1H), 5.18 (ddd, *J*-=2.9, 5.5, 12.3 Hz, 1H), 5.11 (d, *J*=7.5 Hz, 1H), 4.91-4.99 (m, 1H), 4.58 (d, II=12.1 Hz, 1H), 4.37 (d, *J*=5.9 Hz, 1H), 4.10-4.16 (m, 1H), 4.07 (dd, *J*=4.9, 11.5 Hz, 1H), 3.99 (t, *J*=11.7 Hz, 1H), 3.84-3.95 (m, 2H), 3.79 (dd, *J*=6.4, 12.5 Hz, 1H), 3.53 (t, *J*=11.0 Hz, 1H), 3.45 (t, *J*=11.0 Hz, 1H), 2.48-2.57 (m, 2H), 2.09 (ddd, *J*=2.2, 7.1, 13.4 Hz, 1H), 1.66-2.01 (m, 7H), 1.32-1.60 (m, 9H), 1.22 (d, *J*=6.4 Hz, 3H), 1.19 (s, 3H), 1.13 (s, 3H) ppm.
^{13}C NMR (125 MHz, $CDCl_3$):
δ 154.3, 138.6, 137.9, 128.5, 127.9, 126.3, 101.0, 78.4, 74.6, 73.7, 71.1, 70.8, 74.1, 73.7, 52.1, 45.5, 39.3, 32.0, 24.0, 22.7, 15.5 ppm.
FTIR (neat): 3449, 3287, 2936, 2856, 1807, 1734, 1403, 1371, 1301, 1252, 1168, 1136, 1101, 1049, 1009, 977, 913, 807, 777, 732 cm^{-1}.
HRMS (FAB) *m/z* calculated ($C_{29}H_{44}O_{12}Na$) 607.2744; observed 607.2730.
[α] (589 nm, $CDCl_3$) 0.16% solution, +46.8°